

REMARKS

This Amendment, filed in reply to the Office Action dated June 24, 2009, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1, 6 and 13 are amended herewith to improve clarity. Support for the amendments to Claims 1, 6 and 13 can be found throughout the specification as originally filed, and in, for example, the paragraph bridging pages 18 and 19, and Example 1. Claim 15 is canceled herewith without prejudice or disclaimer.

No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Objections to the Claims

On page 3 of the Office Action, Claim 13 is objected to as allegedly being unclear.

Specifically, the Examiner contends that recitation of “producing an aqueous solution of 2-acetyl-butyrolactone [] into 5- hydroxy-2-pentanone” is unclear because reactions are performed, rather than produced. The Examiner suggests that Claim 13 be amended to recite “reducing an aqueous solution of 2-acetyl-butyrolactone [] into 5-hydroxy-2-pentanone.”

Solely to advance prosecution, and without acquiescing in the rejection, Applicants herewith amend Claim 13 to recite “reducing an aqueous solution of 2-acetyl- γ -butyrolactone ... by acid hydrolysis to produce an aqueous solution containing 5-hydroxy-2- pentanone.” Applicants respectfully submit that the amendment overcomes the objection.

Withdrawal of the objection is respectfully requested.

Claim 13 is Definite Under 35 U.S.C. § 112, Second Paragraph

On page 3 of the Office Action, Claim 13 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

Specifically, the Examiner takes the position that recitation of “optionally” in Claim 13 renders the claim indefinite, stating that “it is unclear whether the limitation(s) following the phrase are part of the claimed invention,” citing M.P.E.P. § 2173.05(d) in support of this contention.

Initially, Applicants maintain that Claim 13 is definite because no ambiguity arises as to which alternatives are covered by use of the term “optionally,” and because one of ordinary skill in the art would readily understand the bounds of the claim language, *i.e.*, that the claimed process either employs acid hydrolysis without neutralization, or acid hydrolysis and neutralization. Nevertheless, in the interest of compacting prosecution, and without acquiescing in the rejection, Applicants herewith amend Claim 13 to remove recitation of “and optionally neutralization thereof.” Applicants respectfully submit that the amendments to Claim 13 overcome the rejection.

Withdrawal of the rejection is respectfully requested.

Claims 1 and 10 are Adequately Described Under 35 U.S.C. § 112, First Paragraph

1. On page 4 of the Office Action, Claims 1, 10 and 15 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description.

In making the rejection, the Examiner appears to construe recitation of “ability” in Claim 1 to impart a claim scope that does not actually require the recited cells to produce the recited reducing enzyme. In addition, the Examiner appears to construe the language of Claim 1 such

that only the “acetone-dried cells” need be of the recited microorganism that follows; the Examiner appears to suggest that the “cultured cells, crude extract [and] lyophilized cells” need not be of the microorganisms recited in Claim 1. The rejection also appears to be predicated, in substantial part, on an alleged disconnect between the claimed reduction process, and how the microorganism relates to the process. Specifically, the Examiner states that “such total detachment provides a generic embodiment where *any* activity to produce the reduction is allowed, as long [as] one of these other generic compositions are present.” (Emphasis added.) The Examiner thus appears to suggest that Claims 1 and 10 encompass reduction by *any* means, so long as a microorganism that has the “ability” to produce one of the recited enzymes is present in the reaction.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants note that Claim 15 is canceled herewith, without prejudice or disclaimer, mooted the rejection of this claim.

Turning to the substance of the rejection, Applicants respectfully point out that Claim 1 as amended recites that the claimed asymmetric reduction of 5-hydroxy-2-pentanone is catalyzed by an enzyme comprising the amino acid sequence of the reducing enzyme encoded by a vector selected from the group consisting of: pNTS1G of *Escherichia coli* HB101 (pNTS1G)(FERM BP-5835); pNTFPG of *Escherichia coli* HB101 (pNTFPG)(FERM BP-7117); pNTDRG1 of *Escherichia coli* HB101 (pNTDRG1)(FERM BP-08458); pNTRS of *Escherichia coli* HB101 (pNTRS)(FERM BP-08545); or pNTRGG1 of *Escherichia coli* HB101 (pNTRGG1)(FERM BP-7858). (Emphasis added.) Thus, contrary to the Examiner’s assertion that Claim 1 encompasses reduction by any means, Claim 1 as amended recites that the reducing reaction is catalyzed by

the enzymes produced by the recited vectors. Support for this amendment can be found throughout the specification as originally filed, and in, for example, the paragraph bridging pages 18 and 19, and in Example 1. In view of the experiments described in Example 1 which experimentally demonstrate asymmetric reduction of 5-hydroxy-2-pentanone using such vectors, one of skill in the art would readily have understood Applicants to be in possession of a method for asymmetrically reducing 5-hydroxy-2-pentanone, catalyzed by an enzyme comprising the amino acid sequence of the reducing enzyme encoded by any of the vectors recited in Claim 1. As such, those of skill in the art would recognize that Applicants were in possession of the presently claimed subject matter.

2. On page 5 of the Office Action, Claims 1, 10 and 15 are further rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description.

In making the rejection, the Examiner appears to take the position that Claim 1 as written encompasses a diverse genus of reducing enzyme “derived” from the recited strains, but that the specification as filed does not provide an adequate written description for such a broad genus; the Examiner contends that the specification as filed only contemplates using specific enzymes isolated from the recited strains, the encoding polynucleotide sequences of which were subcloned and transformed into host microorganisms to produce FERM BP- 5835, 7117, 08485, 08545, and 7858.

The Examiner also appears to suggest that Claim 1 also lacks an adequate written description because the specification does not contemplate using the recited organisms themselves to perform the claimed reaction. Rather, the Examiner contends that the specification

does not extend beyond cloning the specific enzymes from the recited microorganisms, and using the transformants.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants note that Claim 15 is canceled herewith, without prejudice or disclaimer, mooted the rejection of this claim.

Turning to the substance of the rejection, Applicants respectfully disagree that the specification as filed does not contemplate using the recited microorganisms themselves for asymmetric reduction. For example, paragraph [0043] of the specification as filed describes that the enzyme source of the invention may be “cultured microbial cells,” and in paragraphs [0044]-[0046], exemplary organisms therefore are listed, including the microbial species which encompass the strains recited in Claim 1. Thus, Applicants respectfully submit that one of skill in the art would readily appreciate from reading paragraphs [0043]-[0046] and [0054] that using the recited strains in Claim 1 as the enzyme source was part of Applicants’ invention, and that Applicants were therefore in possession of such to satisfy the written description requirement of section 112, first paragraph.

Nevertheless, in the interest of advancing prosecution, Claim 1 is amended herewith to recite that the claimed asymmetric reduction of 5-hydroxy-2-pentanone “is catalyzed by an enzyme comprising the amino acid sequence of the reducing enzyme encoded by a vector selected from the group consisting of: pNTS1G of *Escherichia coli* HB101 (pNTS1G)(FERM BP-5835); pNTFPG of *Escherichia coli* HB101 (pNTFPG)(FERM BP-7117); pNTDRG1 of *Escherichia coli* HB101 (pNTDRG1)(FERM BP-08458); pNTRS of *Escherichia coli* HB101 (pNTRS)(FERM BP-08545); or pNTRGG1 of *Escherichia coli* HB101 (pNTRGG1)(FERM BP-

7858).” Further, Claim 1 as amended does not recite the term “derived,” mooted the aspect of the rejection based thereon. In view of the experiments described in Example 1, discussed *supra*, Applicants respectfully submit that Claim 1 as amended is adequately described under section 112, first paragraph.

Withdrawal of the written description rejections is respectfully requested.

Claim 13 is Patentable Under 35 U.S.C. § 103(a)

On page 7 of the Office Action, Claim 13 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Whitney *et al.* (*Advances in Chemistry*, 1974, 130:270-80) in view of “Morrison and Boyd's Organic Chemistry Text.”

In making the rejection, the Examiner contends that Whitney *et al.* disclose the reduction of 5-hydroxy-2-pentanone by chelated lithium compounds, so as to yield optically active 1,4-pentanediol, citing page 277. The Examiner contends that the resultant compounds exhibit stereoselective reduction, “otherwise the resultant compound would not be optically active.”

The Examiner acknowledges, however, that Whitney *et al.* do not disclose or suggest that the compound to be reduced results from acid hydrolysis of 2-hydroxy-gamma-butyrolactone. However, the Examiner contends that it was well known to those of ordinary skill in the art at the time of the invention that acid hydrolysis of 2-hydroxy-gamma-butyrolactone would yield 2-keto-3-carboxyl-pentanol, and that further acid hydrolysis of the beta keto-carboxylate would eliminate the carboxyl group, citing pages 680-81 of “Morrison and Boyd’s Organic Chemistry Text.” In view of such, the Examiner contends that one of ordinary skill in the art would readily have performed acid hydrolysis to convert 2-acetyl-gamma-butyrolactone into 5-hydroxy-2-pentanone.

Further, the Examiner contends that Applicants' averment of unexpected results is irrelevant because "Applicants have claimed a method in which each compound is exactly the same in structure and the method steps are the same; and hence, no distinctness can be obtained."

Further still, in maintaining the rejection, the Examiner relies on paragraph [0026] of the present specification as published. First, the Examiner contends that a decrease in purity of 5-hydroxy-2-pentanone over time, by dehydration condensation, would have been known to those of ordinary skill in the art at the time of the invention. The Examiner cites to the same paragraph to evidence that acid hydrolysis of 2-acetyl-gamma-butyrolactone in the presence of acid yields 5-hydroxy-2-pentanone, and interprets acid-hydrolysis of 2-acetyl-gamma-butyrolactone as simply another method for producing 5-hydroxy-2-pentanone.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

First, Applicants respectfully disagree that the unexpected result discovered by Applicants needs to be claimed to be relevant to patentability. Relevant law holds that all that is required is *evidence* that the claimed subject matter *possesses* an unexpected property or result, which evidence may be presented *inter alia* in the specification as filed, or submitted in a Rule 132 Declaration, for example.² While the Examiner attempts to rebut Applicants' previous arguments in this regard by asserting that the compound in *In re Wiechart* was necessarily nonobvious because of its *structure*,³ such is a misunderstanding. Specifically, in *In re Wiechart*, the obviousness rejection was predicated on the *structural similarity* of the claimed compound to

² See, for example, *In re Wiechart*, 370 F.2d 927, 152 USPQ 247 (CCPA 1967).

³ "and the compound, being non-obvious is necessarily non-obvious, and it is due to its structure." See page 8 of the outstanding Office Action.

prior art compounds. The court reversed the rejection, not on the basis that the compound was “necessarily non-obvious ... due to its structure,” but rather, because although the compound was not structurally nonobvious, it possessed unexpected androgenic and anabolic activity sufficient to rebut a finding of obviousness based on structural similarity. Indeed, in reversing the rejection, the court, citing *In re Lohr*,⁴ stated that

When a new compound so closely related to a prior art compound as to be structurally obvious is sought to be patented based on the alleged greater effectiveness of the new compound for the same purpose as the old compound, clear and convincing evidence of substantially greater effectiveness is needed.

The Court found the appellant’s showing of 7-fold improvement in androgenic activity was unexpected, and sufficient to rebut the rejection. Like the unexpected result discovered by Applicants, the unexpected property at issue in *In re Wiechart* was not recited in the claim.

Moreover, although the Examiner states that Applicants’ averment of unexpected results is unpersuasive because “Applicants have claimed a method in which each compound is exactly the same in structure and the method steps are the same ... and hence, no distinctness can be obtained,” Applicants submit that such a position improperly focuses on the chemical formulae recited in each step of the claim, rather than the unexpected results produced by the claimed method vis-à-vis the method of Whitney *et al.* Specifically, as Applicants have previously noted, the process recited in Claim 13 produces a 5-hydroxy-2-pentanone product that is substantially, and unexpectedly, purer than that which is produced by the method of Whitney *et al.* Nevertheless, Claim 13 is amended herewith to further clarify that the method steps are

⁴ *In re Lohr*, 317 F.2d 388 (CCPA 1963).

performed on the solutions at each stage, which method produces a product of unexpectedly higher purity than that produced by the method of Whitney *et al.*

The Examiner's contention that Applicants' averment of unexpected results is unpersuasive because Applicants "have claimed a method in which each compound is exactly the same in structure and the method steps are the same, [Emphasis added]" is further inapt because Whitney *et al.* do not make 5-hydroxy-2-pentanone by the presently claimed, *i.e.*, "the same," method steps. In assessing whether the higher purity discovered by Applicants' is unexpected, the Examiner appears to be comparing Applicants' claimed method steps to the method allegedly suggested by the *combination* of references asserted in the rejection. However, such is improper. The law is clear that evidence of unexpected results need only be made with respect to the closest single prior art reference. Applicants are not required to provide a comparison against subject matter that does not exist in the art. See *In re Geiger*, 815 F.2d 686, 689, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987). Indeed, the comparison posited by the Examiner would be comparing the results of Applicants' own invention with the results of Applicants' own invention, which is improper. See *In re Chapman*, 357 F.2d 418, 148 USPQ 711 (CCPA 1966).

Further still, in response to Applicants' previous arguments that one of ordinary skill in the art would not reduce 5-hydroxy-2-pentanone in an aqueous solution by the method described by Whitney *et al.*, the Examiner finds such arguments unpersuasive, allegedly because no specific reasoning and/or evidence was proffered. However, Applicants respectfully submit that specific evidence is unnecessary, as such would have been common knowledge to those of ordinary skill in the art. Specifically, Whitney *et al.* employs LiAlH₄ as the reducing agent, and those having ordinary technical knowledge in the art at the time of the invention were aware that LiAlH₄ is explosive upon contact with water. As such, one of ordinary skill in the art would not

have possessed any motivation to combine the reference disclosures in the manner asserted in the rejection, nor any expectation of success in doing so. The claimed invention is not obvious at least in view of the foregoing.

Moreover, a *prima facie* case of obviousness has not been established also because the Examiner has failed to provide a credible reason that would have prompted a person of ordinary skill in the relevant field to combine the reference disclosures in the manner asserted in the rejection, as is required; the Examiner takes the position that mere “availability” is sufficient reason, however, Applicants respectfully point out that mere availability is insufficient reason or motivation when a plethora of other compounds exist to be tried. *Takeda Chem. Indus. v. Alphaphar Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), *cert. denied*, 128 S.Ct. 1739 (2008). Further, the “Morrison and Boyd's Organic Chemistry Text” cited in the rejection provides no description or suggestion, or incites any expectation, of obtaining 5-hydroxy-2-pentanone from 2-acetyl-gamma-butyrolactone. Thus, any reason to combine the reference disclosures in the manner asserted in the rejection is grounded firmly in impermissible hindsight reconstruction, and cannot form the basis of an obviousness rejection, in whole or in part.

In view of the foregoing, Applicants respectfully submit that Claim 13 is not rendered obvious by the cited references.

Withdrawal of the rejection is respectfully requested.

Claims 1, 10 and 13 are Enabled Under 35 U.S.C. § 112, First Paragraph

On page 10 of the Office Action, Claims 1, 10, 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as allegedly lacking enablement.

In making the rejection, the Examiner acknowledges that the specification is enabling for the enzymes encoded in vectors pNTS1G, pNTFPG, pNTDRG1, pNTRS, and pNTRGG1, for the production of R, R, R, S and S enantiomers, respectively. However, the Examiner contends that the specification lacks enablement for the full scope of Claims 1, 10, 13 and 15.

Specifically, the Examiner contends that the specification is not enabling for *any* crude extract, *any* lyophilized cells, *any* acetone-dried cells, or *any* disrupted enzyme. The Examiner also appears to assert that the specification is not enabling for the full scope of reducing enzyme encompassed by the claims. The rejection appears to be predicated, in substantial part, on an alleged disconnect between the recited reduction reaction, and the recited reducing enzyme, such that the claims allegedly encompass the use of any substance to perform the claimed reaction.

To sustain the rejection, the Examiner appears to suggest that the state of the art at the time of the invention was unpredictable to the extent that one of skill in the art would be unable to predict which enantiomers would be made by any particular enzyme, citing Wada *et al.* (*Journal of Bioscience and Bioengineering*, 1999, 87(2):144-48) and Wada *et al.* (*Bioscience and Biotechnological Biochemistry*, 1998), in support of this contention. In view of this alleged unpredictability, the Examiner contends that it would require undue experimentation to identify which enzymes, and which cells encoding such enzymes, can catalyze the requisite reaction.

Applicants respectfully disagree, and traverse the rejection in view of the following remarks.

Initially, Applicants note that Claim 15 is canceled herewith without prejudice or disclaimer, mooted the rejection of this claim.

Further, Applicants note that Claim 1 as amended recites that the reducing reaction is catalyzed by an enzyme comprising the amino acid sequence of a reducing enzyme encoded by

any of pNTS1G, pNTFPG, pNTDRG1, pNTRS, and pNTRGG1, commensurate with that indicated as enabled subject matter by the Examiner; the Examiner expressly acknowledges that the specification is enabling for the asymmetric reduction of 5-hydroxy-2-pentanone, using the enzymes encoded by these vectors.⁵ Moreover, Applicants respectfully submit that the guidance provided in the specification regarding which isomers are produced by the enzyme of each vector, the art-recognized techniques for recombinant protein purification, and Applicants' experimental demonstration of the asymmetric reduction of 5-hydroxy-2-pentanone in Example 1 (catalyzed by the reducing enzymes produced by each of these vectors), would allow one of skill in the art to practice the full scope of Claim 1 without undue experimentation. Accordingly, Applicants respectfully submit that the full scope of Claims 1 and 10 is enabled subject matter. Moreover, one of skill in the art would understand that these enzymes could be produced by any number of different ways, rather than just from these specific vectors, including *inter alia*, other prokaryotic and eukaryotic expression vectors, and synthetic gene synthesis techniques.

With regard to Claim 13, Applicants respectfully point out that Claim 13 is amended herewith to recite that the reduction is by an enzymatic or non-enzymatic process, and that if the reduction is enzymatic, it is catalyzed by an enzyme comprising the amino acid sequence of a reducing enzyme encoded by any of pNTS1G, pNTFPG, pNTDRG1, pNTRS, and pNTRGG1. Thus, the enzymatic reduction processes encompassed by Claim 13 are enabled for the same reasons as Claim 1 is enabled. With respect to non-enzymatic processes encompassed by Claim 13, Applicants note that one of ordinary skill in the art could readily practice such non-enzymatic methods without embarking on undue experimentation. For example, the present specification

⁵ See page 10 of the outstanding Office Action.

discloses a number of asymmetric reduction techniques that one of ordinary skill in the art could employ to practice the claimed non-enzymatic reducing process. See paragraphs [0037-[0042] of the specification as filed.

In view of the above, Applicants respectfully submit that the full scopes of Claims 1, 10 and 13 are enabled subject matter.

Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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